

### Claim Amendments

Claim 1 (currently amended): An apparatus for incubating and determining the state of individual cells within a plurality of cells comprising:

means for incubating the plurality of cells, the incubating means is a dynamically controlled closed environment in which the cells are grown ~~closed system~~ and remains closed while it is dynamically controlled, which is maintained in a desired condition and in which each individual cell of the plurality of cells can be individually examined over time while the environment is dynamically controlled and maintained in the desired condition, the incubating means including an environment controlling means for dynamically controlling the closed environment of the incubating means; and

means for automatically determining the state of said individual cell of the plurality of cells over time disposed in the incubating means while the environment is dynamically controlled and maintained in the desired condition, said determining means in communication with the incubating means, said determining means includes a computer for automatically determining the state of said individual cell of the plurality of cells over time.

Claims 2-46 (canceled)

Claim 47 (previously presented): An apparatus as described in Claim 124 wherein the imaging means includes means for phase contrast imaging to identify the state of said individual cell over time.

Claim 48 (previously presented): An apparatus as described in Claim 47 wherein the phase contrast imaging means compares images to each other serially to identify the state of the cells.

Claim 49 (previously presented): An apparatus as described in Claim 124 wherein the imaging means acquires two successive fluorescent images of each cell and compares them to each other serially to identify the state of each cell.

Claim 50 (previously presented): An apparatus as described in Claim 124 wherein the imaging means includes antibody type labels with different colors of dyes for use to detect the presence of cell surface markers.

Claim 51 (currently amended): An apparatus for incubating and determining the state of individual cells within a plurality of cells comprising:

means for incubating the plurality of cells, the incubating means is a dynamically controlled closed environment in which the cells are grown ~~closed system and~~

remains closed while it is dynamically controlled, which is maintained in a desired condition and in which each individual cell of the plurality of cells can be examined in real time over time while the environment is dynamically controlled and maintained in the desired condition, the incubating means including an environment controlling means for dynamically controlling the closed environment of the incubating means; and

means for automatically determining the state of said individual cell of the plurality of cells in real time over time disposed in the incubating means, said determining means in communication with the incubating means while the environment is dynamically controlled and maintained in the desired condition, said determining means including a computer for automatically determining the state of said individual cell of the plurality of cells in real time over time.

Claim 52 (previously presented): An apparatus as described in Claim 124 wherein the determining means includes means for determining a biological event in said individual cell.

Claim 53 (previously presented): An apparatus as described in Claim 52 wherein the determining means includes means for determining when a cell has doubled.

Claim 54 (previously presented): An apparatus as described in Claim 53 wherein the determining means includes means for determining what stage a cell is in with respect to doubling.

Claim 55 (previously presented): An apparatus as described in Claim 54 wherein the determining means includes means for determining the stage of the cell based on a metabolic process the cell is experiencing.

Claim 56 (previously presented): An apparatus as described in Claim 55 wherein the determining means identifies the production or degradation of proteins, simple or complex sugars, individual amino acids, individual ions, or individual molecules with respect to both physical presence and biological activity of the cell.

Claim 57 (currently amended): An apparatus for incubating and determining the state of individual cells within a plurality of cells comprising:

means for incubating the plurality of cells, the incubating means is a dynamically controlled closed environment in which the cells are grown ~~closed system~~ and remains closed while it is dynamically controlled, which is maintained in a desired condition and in which each individual cell of the plurality of cells can be examined over time while the environment is dynamically controlled and maintained in the desired condition, the incubating

means including an environment controlling means for dynamically controlling the closed environment of the incubating means; and

means for automatically tracking and identifying division and differentiation of said individual cell from the plurality of cells over time in the incubating means, said incubating means in communication with the tracking and identifying means, the tracking and identifying means including a computer for automatically tracking and identifying division and differentiation of said individual cell from the plurality of cells over time.

Claim 58 (previously presented): An apparatus as described in Claim 127 wherein the biochamber includes a first well in which a first cell is disposed and a second well in which a second cell is disposed, and including means for controlling the division and differentiation of the first cell and the second cell while the cells are in the incubating means.

Claim 59 (previously presented): An apparatus as described in Claim 58 wherein the controlling means controls the division and differentiation of the first cell differently from the way it controls the division and differentiation of the second cell while the cells are in the incubating means.

Claim 60 (previously presented): An apparatus as described in Claim 59 wherein the first cell is a different type of cell than the second cell.

Claim 61 (previously presented): An apparatus as described in Claim 60 wherein the controlling means includes means for limiting differentiation of the daughter cells of the first cell.

Claim 62 (previously presented): An apparatus as described in Claim 61 wherein the identifying means includes means for assessing synergistic or antagonistic effects of different combinations of factors on the cells.

Claim 63 (previously presented): An apparatus as described in Claim 62 wherein the identifying means includes means for identifying kinetic data for rates of cell division and differentiation.

Claim 64 (previously presented): An apparatus as described in Claim 63 wherein the controlling means controls the cell with transcriptional regulators and regulators associated with adherence in cell differences based on time.

Claims 65-69 (canceled)

Claim 70 (currently amended): An apparatus for incubating and determining the state of individual cells within a plurality of cells comprising:

means for incubating a first cell and at least a second cell amongst the plurality of cells, the incubating means is a dynamically controlled closed environment in which the cells are grown ~~closed system~~ and remains closed while it is dynamically controlled, which is maintained in a desired condition and in which the first cell and at least the second cell can be individually examined over time amongst the plurality of cells while the environment is dynamically controlled and maintained in the desired condition, the incubating means including an environment controlling means for dynamically controlling the closed environment of the incubating means;

means for individually controlling automatically the division and differentiation of the first cell and at least the second cell amongst the plurality of cells while the cells are in the incubating means, said controlling means automatically controls the division and differentiation of the first cell differently from the way it controls the division and differentiation of the second cell amongst the plurality of cells while the cells are in the incubating means, the controlling means in communication with the incubating means; and

means for individually tracking and identifying division and differentiation automatically of the first cell and at least the second cell amongst the plurality of cells over time in the incubating means, the tracking and identifying means in communication with the incubating means, the tracking and identifying means including a computer for individually

tracking and identifying division and differentiation automatically of the first cell and at least the second cell amongst the plurality of cells over time.

Claims 71-73 (canceled)

Claim 74 (currently amended): An apparatus for incubating and determining the state of a stem cell within a plurality of cells comprising:

means for incubating the plurality of cells, the incubating means is a dynamically controlled closed environment in which the cells are grown ~~closed system and~~ remains closed while it is dynamically controlled, which is maintained in a desired condition and in which each individual cell of the plurality of cells can be individually examined over time while the environment is dynamically controlled and maintained in the desired condition, the incubating means including an environment controlling means for dynamically controlling the closed environment of the incubating means;

means for automatically determining a desired state of the stem cell within the plurality of cells over time in the incubating means, the determining means connected to the incubating means, the determining means in communication with the incubating means, the determining means including a computer for automatically determining a desired state of the stem cell within the plurality of cells over time; and



means for automatically introducing quiescence media to the stem cell within the plurality of cells in the incubating means when the stem cell is in the desired state to inhibit the proliferation or selected differentiation of the stem cell in the incubating means, said introducing means connected to the incubating means, the introducing means in communication with the incubating means.

Claim 75 (currently amended): An apparatus for incubating and determining the state of individual cells within a plurality of cells comprising:

means for incubating the plurality of cells, the incubating means is a dynamically controlled closed environment in which the cells are grown ~~closed system~~ and remains closed while it is dynamically controlled, which is maintained in a desired condition and in which each individual cell of the plurality of cells can be individually examined over time while the environment is dynamically controlled and maintained in the desired condition, said incubating means having means for controlling the environment about said individual cell over time in the incubating means to maintain the environment about said individual cell over time in a desired condition; and

means for automatically determining the state of said individual cell of the plurality of cells over time in the incubating means, said determining means in communication

with the incubating means, the determining means including a computer for automatically determining the state of said individual cell of the plurality of cells over time.

Claim 76 (previously presented): An apparatus as described in Claim 75 wherein the controlling means includes means for exchanging  $n$  media, where  $n$  is greater than or equal to 2, in the incubating means.

Claim 77 (previously presented): An apparatus as described in Claim 76 wherein the incubating means includes  $m$  wells, where  $m$  is greater than or equal to 2, and the cell is disposed in a first of the  $m$  wells, and the exchanging means exchanges  $n$  media in the first well.

Claim 78 (previously presented): An apparatus as described in Claim 76 wherein  $n$  equals 96.

Claim 79 (previously presented): An apparatus as described in Claim 75 including means for automatically testing for predetermined biological variables and engineered genes with respect to each cell.

Claim 80 (currently amended): An apparatus for incubating and determining the state of individual cells within a plurality of cells comprising:

means for incubating the plurality of cells, the incubating means is a dynamically controlled closed environment in which the cells are grown ~~closed system~~ and remains closed while it is dynamically controlled, which is maintained in a desired condition and in which each individual cell of the plurality of cells can be individually examined over time while the environment is dynamically controlled and maintained in the desired condition;

a robotic means including a robotic arm for automatically dispensing and aspirating different material while said cell of the plurality of cells are disposed in the incubating means; and

means for automatically controlling the environment about said individual cell over time within the plurality of cells in the incubating means to maintain the environment about said individual cell over time within the plurality of cells in a desired condition.

Claim 81 (previously presented): An apparatus as described in Claim 80 including a supply of antigen and a supply of fluorochrome connected to the robotic means so antigen or fluorochrome can be dispensed to the cells in the incubating means.

Claims 82-85 (canceled)

Claim 86 (previously presented): An apparatus as described in Claim 80 wherein the incubating means has wells which hold corresponding cells and wherein the robotic means includes a pipette which transfers media from individual cells to the determining means at predetermined intervals.

Claim 87 (previously presented): An apparatus as described in Claim 80 wherein the robotic means dispenses 1 to 95 microliters of media.

Claim 88 (previously presented): An apparatus as described in Claim 80 including a liquid handling system connected to the robotic means and means for cleaning of the liquid handling system with wash cycles.

Claim 89 (previously presented): An apparatus as described in Claim 86 including P additional pipettes in communication with the wells, each pipette can either aspirate or dispense liquid to the wells, where P is an integer greater than or equal to 2.

Claim 90 (previously presented): An apparatus as described in Claim 86 including a syringe pump connected to the pipette to aspirate or dispense liquid through the pipette.

Claim 91 (previously presented): An apparatus as described in Claim 90 wherein the syringe pump includes a 250 microliter syringe pump.

Claim 92 (previously presented): An apparatus as described in Claim 80 wherein the robotic means includes a probe which, when placed in a well, identifies how much fluid is in the well.

Claim 93 (previously presented): An apparatus as described in Claim 86 wherein the pipette can remove tissue culture media, nutrients or proteins from a well.

Claim 94 (previously presented): An apparatus as described in Claim 124 wherein the biochamber includes a plate with a plurality of wells in which the cells are disposed, and the imaging means counts the number of cells in each well of the plurality of wells.

Claim 95 (previously presented): An apparatus as described in Claim 80 wherein the determining means analyzes tissue culture media in a well with either biochemical, immuno chemical, biological or chemical assays.

Claim 96 (previously presented): An apparatus as described in Claim 124 wherein the imaging means uses pattern recognition to correlate a state of a cell with a particular metabolic process of the cell.

Claim 97 (previously presented): An apparatus as described in Claim 80 including a determining means for automatically testing for production or degradation of proteins, simple or complex sugars, individual amino acids, individual member ions, individual molecules with respect to both physical presence and biological activity in the incubating means, said determining means connected with the incubating means, said determining means including a computer.

Claim 98 (canceled)

Claim 99 (previously presented): An apparatus as described in Claim 86 wherein operation of the pipette is optimized when the fluid forces applied to the cells are minimized while retaining a sufficient flow rate for medium exchange.

Claim 100 (previously presented): An apparatus as described in Claim 80 including a determining means for obtaining kinetic data for the rates of cell division differentiation, said determining means connected to the incubating means.

Claims 101 and 102 (canceled)

Claim 103 (previously presented): An apparatus as described in Claim 124 wherein the imaging means recognizes when a cell doubles in the incubating means by pattern recognition.

Claim 104 (previously presented): An apparatus as described in Claim 1 wherein the determining means includes a plurality of dyes, each dye associated with a different cell surface marker, to identify cell surface markers on a cell.

Claims 105-113 (canceled)

Claim 114 (currently amended): An apparatus for culturing and analyzing cells, the apparatus comprising:

a biochamber having a plurality of cell housing containers in which cells to be cultured may be introduced therein, the biochamber being a dynamically controlled closed system in which the cells are grown, the biochamber having an environment controlling means for dynamically controlling the closed environment of the biochamber;

a liquid handling system for providing exchange of media to the cells while the cells are in the biochamber, the liquid handling system in fluid communication with the plurality of cell housing containers in the biochamber;

an image recognition system for analyzing the state of each cell of the cells over time that are disposed in the plurality of cell housing containers in the biochamber, the image recognition system utilizing image recognition software;

a stage for supporting the biochamber, the biochamber, liquid handling system and image recognition system being in movable registration with respect to one another whereby the liquid handling system and image recognition system can access different cell housing containers; and

a system controller capable of regulating interaction between the biochamber, liquid handling system, image recognition system and stage.

Claim 115 (previously presented): The apparatus for culturing and analyzing cells according to Claim 114, wherein the image recognition system further includes a microscope comprising a camera for deriving images from the cells within the plurality of cell housing containers.



Claim 116 (previously presented): The apparatus for culturing and analyzing cells according to Claim 115, wherein the derived images are processed by the image recognition software to determine cellular characteristics of the cells.

Claim 117 (previously presented): The apparatus for culturing and analyzing cells according to Claim 116, wherein upon determination of particular cellular characteristics of the cells, the system controller is prompted to actuate the liquid handling system to provide exchange of media to the cells.

Claim 118 (previously presented): The apparatus for culturing and analyzing cells according to Claim 114, wherein the liquid handling system aspirates, irrigates and dispenses the media to the cells.

Claim 119 (previously presented): The apparatus for culturing and analyzing cells according to Claim 114, wherein the liquid handling system further includes a plurality of pipettes for providing the exchange of media to the cells, the plurality of pipettes being movable along X, Y and Z dimensions with respect to the plurality of cell housing containers.

Claim 120 (previously presented): The apparatus for culturing and analyzing cells according to Claim 114, wherein the stage displaces at least one of the plurality of cell

housing containers with respect to the liquid handling system and the image recognition system.

Claim 121 (previously presented): The apparatus for culturing and analyzing cells according to Claim 114, wherein the image recognition system is capable of determining varying cellular characteristics and the system controller regulates the biochamber and liquid handling system in response to the determined cellular characteristics.

Claim 122 (previously presented): The apparatus for culturing and analyzing cells according to Claim 114, wherein the biochamber is respectively displaceable to both the liquid handling system and the image recognition system.

Claim 123 (previously presented): The apparatus for culturing and analyzing cells according to Claim 114, wherein the biochamber is displaceable along X and Y lateral dimensions and the liquid handling system and image recognition system are displaceable along a Z dimension.

Claim 124 (previously presented): An apparatus as described in Claim 125 wherein the determining means includes an imaging means which images said individual cell of the plurality of cells over time in the biochamber.

Claim 125 (previously presented): An apparatus as described in Claim 1 wherein the incubating means includes a housing having a biochamber.

Claim 126 (previously presented): An apparatus as described in Claim 51 wherein the incubating means includes a housing having a biochamber.

Claim 127 (previously presented): An apparatus as described in Claim 57 wherein the incubating means includes a housing having a biochamber.